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(71) Applicant *(for all designated States except US)*: **ARAKIS LTD.** [GB/GB]; Chesterford Research Park, Little Chesterford, Saffron Walden, Essex CB10 1XL (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BREW, John** [GB/GB]; Arakis Ltd., Chesterford Research Park, Little Chesterford, Saffron Walden, Essex CB10 1XL (GB). **BANNISTER, Robin, Mark** [GB/GB]; Arakis Ltd., Chesterford Research Park, Little Chesterford, Saffron Walden, Essex CB10 1XL (GB). **BAXTER, Andrew, Douglas** [GB/GB]; Arakis Ltd., Chesterford Research Park, Little Chesterford, Saffron Walden, Essex CB10 1XL (GB). **ROTHAUL, Alan** [GB/GB]; Arakis Ltd., Chesterford Research Park, Little Chesterford, Saffron Walden, Essex CB10 1XL (GB). **LYNE, Michael, Harvey** [GB/GB]; Arakis Ltd., Chesterford Research Park, Little Chesterford, Saffron Walden, Essex CB10 1XL (GB).

(74) Agent: **GILL JENNINGS & EVERY**; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).

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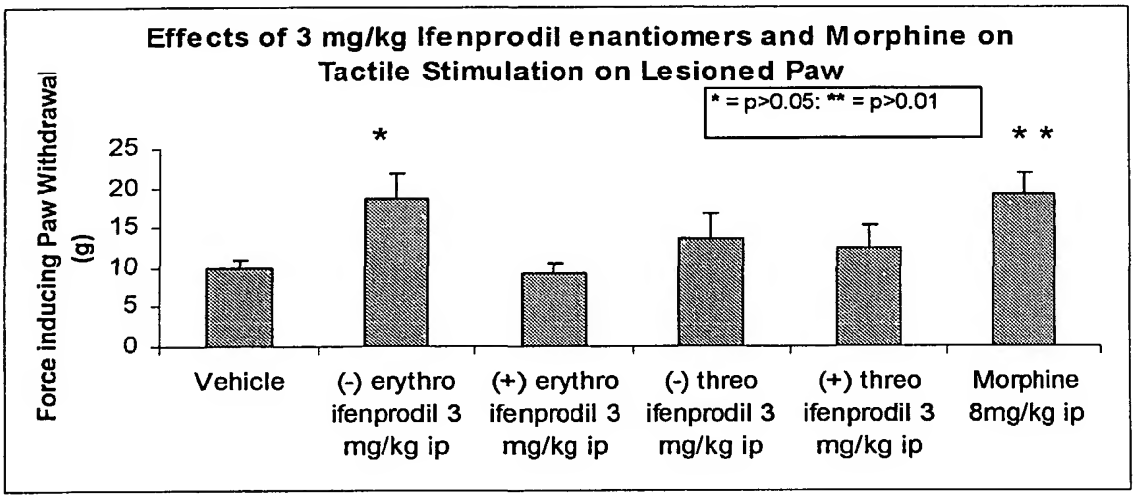
(54) Title: THE TREATMENT OF PAIN WITH IFENDROPIL



(57) Abstract: Ifenprodil is useful for the treatment of pain, *e.g.* on administration intranasally or by another route that avoids first-pass metabolism.

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THE TREATMENT OF PAIN WITH IFENPRODIL

Field of the Invention

This invention relates to the use of a known compound for the treatment of pain.

Background of the Invention

N–methyl-D-aspartate (NMDA) receptor antagonists have been long known to exhibit anti-nociceptive effects, and a number have proven efficacy in the treatment of a number of neuropathies, including postherpetic neuralgia, central pain caused by spinal cord injury and phantom limb pain. The NMDA receptor antagonist dextrorphan is disclosed for the treatment of pain in EP-A-0615749 and also, along with a number of other such compounds (including ifenprodil), in WO-A-97/14415. Unfortunately, most agents which block the NMDA receptor also induce unacceptable side-effects at analgesic doses, including memory impairment, ataxia, hallucinations and dysphoria, which prohibit their widespread use.

Ifenprodil, i.e. 2-(4-benzylpiperidino)-1-(4-hydroxyphenyl)-1-propanol, selectively blocks NR2B-containing NMDA receptors in a voltage-independent and non-competitive manner (Gallagher *et al.*, 1996, J. Biol. Chem. 271(16):9603-9611) and exhibits anti-nociceptive activity in animal models of acute and chronic pain (Taniguchi *et al.*, 1997, Brit. J. Pharmacol. 122, 809-812; Boyce *et al.*, 1999, Neuropharmacology 38:611-623). Ifenprodil (as ifenprodil tartrate) is commercially available as a racemic mixture of the *erythro* diastereomer.

Ifenprodil also exhibits potent alpha-1 adrenergic receptor binding properties (Chenard *et al.*, 1991, J. Med. Chem. 34 (10):3085-3090) which can cause hypotension and syncope in some recipients. It is also reported by Chenard *et al.* that the *threo* isomers of ifenprodil have selectivity for the NMDA receptor over the alpha-1 adrenoreceptor.

Summary of the Invention

The present invention is based on the discovery that ifenprodil has utility in the treatment of pain, including neuropathic pain and migraine headache.

As suggested above, it has been thought in the past that (-)-*threo* ifenprodil has improved NMDA activity over the other enantiomers, and that this would produce a significant improvement in efficacy. Surprisingly, it has now been demonstrated that (-)-*threo* ifenprodil does not produce a significant increase in efficacy over the other enantiomers in a model of neuropathic pain. However, it has been shown that this enantiomer has lower hypotension liability (alpha1-adrenoceptor antagonism), which will improve its side-effect profile over the other enantiomers.

Description of Preferred Embodiments

Ifenprodil has two chiral centres. Any reference herein to ifenprodil should be understood as a reference to any enantiomer or mixture thereof. Any enantiomer may be substantially free of others, e.g. in an enantiomeric excess of at least 80%, preferably at least 90% and more preferably at least 95%. Similarly, any mixture of diastereomers may be substantially free of the other. The *threo* form, and in particular the (-)-*threo* form, may be preferred in certain cases; the (-)-*erythro* form may be preferred in others.

The ifenprodil may be in the form of the free base or any pharmaceutically acceptable salt, e.g. the tartrate, or in the form of a metabolite or prodrug. Such forms are known to those of ordinary skill in the art.

The active agent may be administered by, for example, the oral, topical, dermal, ocular, intravenous, intraarticular, rectal, vaginal, inhalation, intranasal, sublingual or buccal route. The amount of active ingredient that is used can be chosen by the skilled person having regard to the usual factors.

For use, the active agent is typically formulated, e.g. with a conventional diluent or carrier, or as a patch, as a medicament adapted to be delivered by the chosen route. Such formulations are known to those skilled in the art, and will be chosen according to the usual considerations such as the potency of the drug, the severity of the condition and the route of administration.

Ifenprodil is preferably administered intranasally, buccally or by any route that avoids first-pass metabolism. Indeed, nasal delivery introduces significant concentrations of ifenprodil and its isomers to NMDA receptors whilst reducing side-effects caused by the unwanted alpha-1 adrenoreceptor-binding activity.

In this context, a typical daily dose is less than 60 mg, e.g. 1 to 50 mg, ifenprodil; a higher dose, e.g. up to 500 mg, may be used, especially if first-pass metabolism is not avoided.

In particular, it would be of benefit to administer ifenprodil in a manner that reduced peripheral exposure to vascular smooth muscle (minimise effect on vascular tone), while maximising the concentrations in the CNS (maximise analgesia). This may be done by nasal delivery, reducing systemic load, while maximising the concentration of drug in the CNS. By way of example only, a composition for intranasal delivery comprises, in addition to ifenprodil, one or more of a solubility enhancer such as propylene glycol, a humectant such as mannitol, a buffer and water. A mucoadhesive agent may also be used.

Ifenprodil has very poor pharmacokinetics, with very high first-pass metabolism (5% bioavailability and a short half life; t1/2 1 hour). Consequently, administering ifenprodil orally, to treat a chronic condition like neuropathic pain, may require high and frequent doses. Dermal administration, e.g. by the use of a dermal patch, allows chronic dosing of this compound, while avoiding first-pass metabolism and so lowering the dose. Additionally, there is the potential of removing the dose from the circulation rapidly at the end of the treatment period.

It will often be advantageous to use ifenprodil in combination with another drug used for pain therapy. Such another drug may be an opiate or a non-opiate such as baclofen. Especially for the treatment of neuropathic pain, coadministration with gabapentin is preferred.

The following experiments provide the evidence on which the present invention is based.

In a test on the effect of agents on thermal stimulation of the lesioned paw, ifenprodil (at 3, 10 and 30 mg/kg ip) was more effective than gabapentin (at 30 mg/kg ip) and almost as effective as morphine (at 8 mg/kg ip). Such tests showed that (-)-*threo*-ifenprodil was the most effective enantiomer (at 3 mg/kg ip).

Evidence of the incorrect conclusion reached by Chenard *et al.*, 1991, *supra*, is provided by experiments conducted in a Bennett model (Bennett *et al*, 1988, Pain 33(1):87-107). The results are shown in the accompanying drawing.

The following Example illustrates a composition suitable for intranasal delivery. In this Example, 1-10 mg ifenprodil is included in 100 µl of:

Excipient:	%w/w	
Benzalkonium chloride	0.02	Preservative
Propylene Glycol	25	Solubility Enhancer
Mannitol	15	Humectant
HNa_2PO_4 (0.2M)	25.2	
Citric Acid (0.1M)	10.0	
Deionised water	24.6	(pH6.5 buffer)

CLAIMS

1. Use of ifenprodil for the manufacture of a medicament for the treatment of pain.

2. Use according to claim 1, for the treatment of neuropathic pain.

3. Use according to claim 1, for the treatment of migraine.

4. Use according to any preceding claim, wherein the ifenprodil is in the form of either or both *threo* enantiomers.

5. Use according to claim 4, wherein the ifenprodil is (-)-*threo*-ifenprodil.

6. Use according to any of claims 1 to 3, wherein the ifenprodil is (-)-*erythro*-ifenprodil.

7. Use according to any preceding claim, wherein the medicament is for administration via a route that avoids first-pass metabolism.

8. Use according to claim 6, wherein the route is intranasal.

9. Use according to claim 6, wherein the route is dermal.

10. Use according to any of claims 7 to 9, wherein the medicament contains less than 60 mg ifenprodil.

11. A composition, suitable for intranasal delivery, which comprises an aqueous solution of ifenprodil, a solubility enhancer and a humectant.

12. A composition according to claim 11, wherein the ifenprodil is (-)-*threo*-ifenprodil.

13. A composition according to claim 11, wherein the ifenprodil is (-)-*erythro*-ifenprodil.

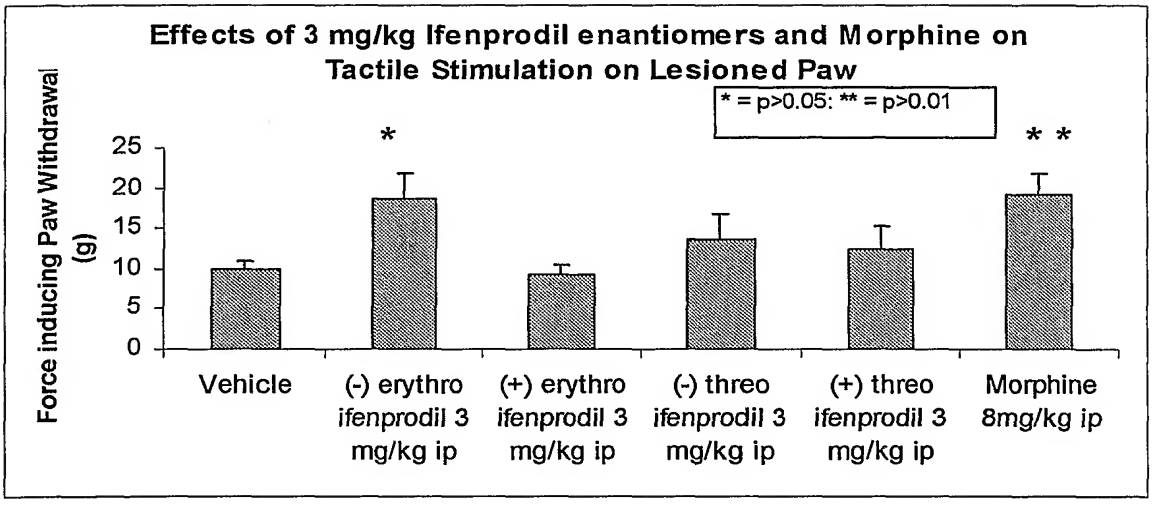
Effects of 3 mg/kg Ifenprodil enantiomers and Morphine on Tactile Stimulation on Lesioned Paw
* = p>0.05: ** = p>0.01
Force inducing Paw Withdrawal (g)
25
20
15
10
5
0
*
* *
Vehicle
(-) erythro ifenprodil 3 mg/kg ip
(+) erythro ifenprodil 3 mg/kg ip
(-) threo ifenprodil 3 mg/kg ip
(+) threo ifenprodil 3 mg/kg ip
Morphine 8mg/kg ip

Figure 1

INTERNATIONAL SEARCH REPORT

Interna Application No
PCT/GB 03/01906

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 14415 A (FAULDING F H & CO LTD ;SMITH IAN KEITH (AU); HEINICKE GRANT WAYNE) 24 April 1997 (1997-04-24) cited in the application the whole document	1-13
X	CHENARD B L ET AL: "SEPARATION OF ALPHA1 ADRENERGIC AND N-METHYL-D-ASPARTATE ANTOGONISTACTIVITY IN A SERIES OF IFENPRODIL COMPOUNDS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 34, no. 10, 1 October 1991 (1991-10-01), pages 3085-3090, XP000564617 ISSN: 0022-2623 * Experimental section *	11-13

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 July 2003	30/07/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Baston, E

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INTERNATIONAL SEARCH REPORT

Interna I Application No
PCT/GB 03/01906

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	CHIZH BORIS A ET AL: "Supraspinal vs spinal sites of the antinociceptive action of the subtype-selective NMDA antagonist ifenprodil" NEUROPHARMACOLOGY, PERGAMON PRESS, OXFORD, GB, vol. 40, no. 2, 2001, pages 212-220, XP002192014 ISSN: 0028-3908 the whole document	1-13
X	TAMIZ A P ET AL: "STRUCTURE-ACTIVITY RELATIONSHIPS FOR A SERIES OF BIS(PHENYLALKYL)AMINES: POTENT SUBTYPE-SELECTIVE INHIBITORS OF N-METHYL-D-ASPARTATE RECEPTORS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 41, no. 18, 27 August 1998 (1998-08-27), pages 3499-3506, XP001151638 ISSN: 0022-2623 the whole document	1-13
X	EP 0 698 391 A (SYNTHELABO) 28 February 1996 (1996-02-28) page 3, line 6 - line 16	11-13

INTERNATIONAL SEARCH REPORT

ation on patent family members

Interna | Application No
PCT/GB 03/01906

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9714415 A	24-04-1997	AU 708408 B2	05-08-1999
		AU 7207896 A	07-05-1997
		WO 9714415 A1	24-04-1997
		EP 0858334 A1	19-08-1998
		US 6194000 B1	27-02-2001
EP 0698391 A	28-02-1996	FR 2722989 A1	02-02-1996
		CA 2154906 A1	30-01-1996
		EP 0698391 A1	28-02-1996
		FI 953622 A	30-01-1996
		JP 8040902 A	13-02-1996
		NO 953003 A	30-01-1996
		US 5543421 A	06-08-1996